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DIGOXIN INTERACTIONS WITH MEDICATIONS USED IN CONGESTIVE HEART FAILURES AND OTHER CO-MORBID DISEASES: AN IDENTIFICATION OF PATIENTS REQUIRING CONSTANT DRUG THERAPY MONITORING AND VIGILANCE

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ABSTRACT

Background: Digoxin has narrow therapeutic index and many drug combinations are capable of affecting both its pharmacokinetic and pharmacodynamics profile, which may lead to lethal outcomes. **Objectives:** The objectives were to assess potential interactions between digoxin and other medications and to evaluate its degree, clinical outcomes as well as identify patients that may require constant monitoring and vigilance. **Methods:** The cross-sectional and prospective study involves the evaluation of digoxin interaction with other medications using online drug interaction software checkers developed by Medscape.com, Drug.com, Drugbank.com and Epocrates. Patients were sampled from both out-patients department during clinic visits and also hospitalized In-Patients. **Results:** Digoxin was recommended to 71(31.1%) patients and combined with loop diuretic in 51(22.4%) cases and other combinations such as potassium sparing diuretics 44(19.3%), thiazide diuretics 11(4.8%), carvedilol 43(19.7%), ACEI 35(15.4%), ARB 9(3.9%), calcium channel blocker 6(2.6%), anti-platelets 15(6.6%), and with statins, antacid and calcitriol in 5(2.2%) proportion each; and with anti-gout/arthritis medications 3(1.3%). Digoxin co-use in patients with other co-morbidities was significantly different from similar patients who do not use digoxin in hypertension (X^2=17.38; P<0.001); anaemia (x^2=4.97, p=0.026); CKD (x^2=10.37, p<0.001) and stroke (x^2=10.54, p<0.001). A cumulative total of 574 interactions were identified in the study. Carvedilol and spironolactone accounted for the highest multiple of interactions (being 4 each). Atenolol has tripled multiple interactions with digoxin while bendroflumethiazide, calcium carbonate, furosemide and aspirin were all in the multiple of 2 each. A total of 239 (41.6%) interactions were pharmacokinetics in nature while 335 (58.4%) are pharmacodynamics. Carvedilol 129(54.0%) accounted for the majority of pharmacokinetic interactions while furosemide 102(30.4%) accounted for majority of pharmacodynamics interactions. Of the 239 pharmacokinetics interactions, absorption, metabolism and excretion accounted for 48(20.1%), 54(22.6%) and 137(57.3%) respectively and for the 335 pharmacodynamics interactions; potentiation, synergism/addictive and antagonistics interactions accounted for 52 (15.5%), 219(65.4%) and 64(19.1%) respectively. The clinical outcome arising from the interactions are increase in serum levels of digoxin 121(19.5%), increase in digoxin effects through synergism 61(9.8%), increased bradycardiac effects 24(7.2%), enhanced AV block 6(1.0%), enhanced arrhythmogenic effects 5(0.8%), false elevation in digoxin assay 10(1.6%), enhanced adverse effects/toxicity of digoxin 62(10.0%), decreased therapeutic effects of digoxin 44(7.1%), decreased excretion of digoxin 90(14.5%), decreased metabolism of digoxin 51(8.2%), increased K^+ levels 18(6.2%) and other electrolytes problems 62 (10.0%). Several interventions will be needed such as monitoring digoxin 154(50.3%), dose reduction by 15-30% of digoxin 98(32.0%) or even by 30-50% 29(9.5%), exercising caution in digoxin use 5(1.6%), and total avoidance or use of alternative agents 10(3.3% each). **Conclusion:** Several clinical outcomes resulting from digoxin interactions are capable of causing serious untoward adverse effects and toxicity to several patients. Many interactions from the combinations are rated serious and should have been avoided while others are moderately significant. These patients would therefore requires several therapeutic approach such as decreasing the dose of digoxin, monitoring the levels, monitoring toxicity and ECG monitoring as well symptomatic monitoring.

KEYWORDS: Digoxin, digoxin interactions, congestive heart failures, digoxin-spironolactone, carvedilol.

INTRODUCTION

Drug interactions can take the forms of drug-drug interaction (DDI), drug-food interaction (DFI), drug-herb interaction (DHI), and drug-disease interaction (DDis), and Drug-environment interaction (DEI). DDIs is said to occur when two or more drugs interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered. Drug-drug interactions can be beneficial and gainfully explore to achieve desired therapeutic advantage when fully comprehended. However, most DDIs may also constitute threat and may present with harmful outcomes. It has been estimated that DDIs is responsible for 2.8% of hospitalizations in older patients and an estimated cost of more than one billion US dollar annually.[1,2] DDIs may increase with corresponding increase in health care use.[3] Adverse drug reactions resulting from DDIs have been reported to cause up to 1% of all hospital admissions and 0.05% of emergency department visits and 0.6% of the hospital admissions and 0.1% of re-hospitalizations.[4,5] DDIs have also caused increased hospital stay and cost of care and may cause addition stress on the over stretched health facilities in some quarters.

Drug-drug interaction can affect any patient requiring more than one medication at a time. Certain drug characteristics make the effects of DDI to be pronounced. Digoxin is one of the drugs with narrow therapeutic index and as such drug combination affecting both its pharmacokinetic and pharmacodynamics profile could present a lethal outcome. According to some authors, Potential for drug interaction is higher with cardiac drugs,[6] or in cardiology unit of some hospitals.[7]

Digoxin in one of the mainstay drugs in patients with heart failure. The agents owe its usefulness because of its multiple effects such as an enhanced cardiac contractility, improved baroreceptor function, decrease sympathetic tone and reduction in neuro-hormone concentration.[8,9] Among other benefits of digoxin, there is also relieve of congestion symptoms, heart rate control in atrial fibrillation, ventricular function enhancement, decrease the occurrence of hospitalization for worsening of HF and reduce deteriorations in the clinical status of HF patients.[10-12] Patients with symptomatic HF and HF patients with AF and a left ventricular ejection fraction (LVEF) of less than 40% will benefit from the use of digoxin.[13]

AIM AND OBJECTIVES

The objectives were to assess potential interactions between digoxin and other medications and to evaluate its degree, potential clinical outcomes as well as to identify patients that may require constant monitoring and vigilance.

MATERIALS AND METHODS

The study was conducted at the University of Maiduguri Teaching Hospital, Maiduguri, Borno State; which is situated at the North-East zone of Nigeria. The Tertiary hospital runs several clinics including Cardiology Clinics. The cross-sectional and prospective study involves the evaluation of drug interaction involving digoxin and other medications prescribed for patients with congestive heart failure. Online drug interaction software checkers developed by Medscape.com, Drug.com, Drugbank.com and Epocrates were used complimentarily to evaluate digoxin combinations with other prescriptions ordered for individual patient. The CHF Patients were sampled from out-patients and in-patients departments as well as during patients' clinic visits.

TABLES OF RESULTS

Table 1: Age of Patients with Digoxin medication as component of drug management.

Age distribution	Digoxin used (%)	Digoxin not used (%)	TOTAL (%)
0.0-10.0	0 (0)	19 (12.1)	19 (8.3)
10.1-20.0	5 (7.0)	4 (2.5)	9 (3.9)
20.1-30.0	11 (15.5)	14 (8.9)	25 (11.0)
30.1-40.0	14 (19.7)	38 (24.2)	52 (22.8)
40.1-50.0	9 (12.7)	26 (16.6)	35 (15.4)
50.1-60.0	17 (23.9)	30 (19.1)	47 (20.6)
60.1-70.0	8 (11.3)	21 (13.4)	29 (12.7)
70.1-80.0	7 (9.9)	5 (3.2)	12 (5.3)
TOTAL	71 (100)	157 (100)	228 (100)

X^2=18.798; p=0.009

Table 2: Demographic Characteristics and Lifestyle of Patients

Characteristics	Variable	Frequency	Percentage
Gender	Male	82	36.0
	Female	146	64.0
Religion	Christian	26	11.4
	Islam	202	88.6

Marital Status	Single	34	14.9
	Married	179	78.5
	Widow	15	6.6
Educational Status	Educated	215	94.3
	Uneducated	13	5.7
Occupational Status	Employed	79	34.9
	Unemployed	138	60.5
	Retired	11	4.8
Smoking Habit	Smoker	10	4.4
	Non-smoker	218	95.6
Alcohol Intake	Drinks	0	0
	Does not drink	228	100
Exercise Habit	Regular	8	3.5
	Not-regular	65	28.5
	Not at all	155	68.0

Table 3: Patients with CHF requiring the use of digoxin and other Co-morbid conditions.

Comorbid diseases	Cases (n=228) Freq. (%)	Digoxin Usage Freq.	Digoxin not used Freq.	Total digoxin used	X^2/FET & p-value
Obesity	2 (0.9)	0	2	71	FET=0.473
Hypothyroidis	2 (0.9)	0	2	71	FET=0.473
Hypertension	80 (35.1)	11	69	71	X^2=17.38; p<0.001
CAD	43 (18.9)	14	29	71	X^2=0.050; p=0.824
Anaemia	57 (25.0)	11	46	71	X^2=4.97; p=0.026
Arthritis	23 (10.1)	4	19	71	FET=0.100
Arrhythmia	2 (0.9)	0	2	71	FET=0.473
CKD	57 (25.0)	8	49	71	X^2=10.37; p=0.001
Dyslipidaemia	21 (9.2)	5	16	71	X^2=; p=0.446
Migraine	2 (0.9)	0	2	71	FET=0.473
Stroke	23 (10.1)	14	9	71	X^2=10.54; p=0.001
Tuberculosis	1 (0.4)	0	1	71	FET=0.689

Table 4: Drugs used by CHF patients and the proportions co-administered with digoxin.

Drugs Used in CHF/Comorbid diseases	Proportion Used in the study	Proportion used with Digoxin
Loop Diuretics(Frusemide, Torsemide)	168 (70.2)	51 (22.4)
Potassium Sparing Diuretic (spironolactone)	72 (31.6)	44 (19.3)
Thiazide (Bendro, hydroclorthiazide)	20 (8.8)	11 (4.8)
Carvedilol/atenolol	86 (37.7)	45 (19.7)
ACEI(Lisinopril, captopril)	127 (55.7)	35 (15.4)
ARB (losartan)	40 (17.5)	9 (3.9)
Digoxin	71 (31.1)	-
Vasodilator (hydralazine)	3 (1.3)	0 (0)
CCB (Amlodipine, Nifedipine)	48 (21.1)	6 (2.6)
Anti-platelets (vasoprin, clopidegrel, warfarin)	67 (29.4)	15 (6.6)
Haematinics (folic acid, fersolate)	100 (43.9)	20 (8.8)
Statin(artovastatin, simvastatin, rusovastatin)	21 (9.2)	5 (2.2)
Anti-Tuberculosis medication(INH, PZI, RFP, ETM)	4	0 (0)
Antacid ($CaCO_3$)	47 (20.6)	5 (2.2)
Calcitriol	53 (23.2)	5 (2.2)
Anti-Gout and anti-arthritis (colchicine, allopurinol)	24 (10.5)	3 (1.3)
Antidepressant	2(0.9)	0 (0)
TOTAL		**254**

Key: INH=isoniazid; PZI=pyrazinamide; RFP=rifampicin; ETM=ethambutol; $CaCO_3$=calcium carbonate; ARB=angiotensin receptor blocker; ACEI=angiotensin converting enzyme inhibitor

Table 5: Number of Drugs per prescription interacting with Digoxin.

Nos. of drugs interacting with Digoxin per prescription	Frequency	Percentage (%)
One	11	4.8
Two	23	10.1
Three	24	10.5
Four	11	4.8
Five	1	0.4
Six	1	0.4
None	157	68.9
TOTAL	228	100.0

Table 6: Some specific drugs interaction with digoxin.

Drug Interactions	Nos of Interactions	Nos of patients	Total (Cumulative)
Digoxin-captopril	1	6	6
Digoxin-Lisinopril	1	29	29
Digoxin losartan	1	9	9
Digoxin-Carvedilol	4	43	172
Digoxin-Spironolactone	4	44	176
Digoxin bendro/HCT	2	11	22
Digoxin-nifedipine	1	6	6
Digoxin-Calcium carbonate	2	5	10
Digoxin-Calcitriol	1	5	5
Digoxin-Furosemide	2	51	102
Digoxin-Atenolol	3	2	6
Digoxin-Aspirin	2	9	18
Digoxin-Clopidogrel	1	6	6
Digoxin-Atorvastatin	1	5	5
Digoxin-Colchicine/allopurinol	1	3	3
TOTAL	26	234	574

Table 7: Specific types of digoxin-drug interactions.

Drug Interactions	Pharmacokinetics	Pharmacodynamics	Total (%)
Digoxin-captopril	6	0	6 (1.0)
Digoxin-Lisinopril	29	0	29 (5.0)
Digoxin losartan	0	9	9 (1.7)
Digoxin-Carvedilol	129	86	215(37.3)
Digoxin-Spironolactone	44	88	132(22.9)
Digoxin bendro/HCT	0	22	22 (3.8)
Digoxin-nifedipine	2	0	2 (0.3)
Digoxin-amlodipine	4	0	4 (0.7)
Digoxin-Calcium carbonate	5	5	10 (1.7)
Digoxin-Calcitriol	5	0	5 (0.9)
Digoxin-Furosemide	0	102	102(17.7)
Digoxin-Atenolol	0	6	6 (1.0)
Digoxin-Aspirin	9	9	18 (3.1)
Digoxin-clopidogrel	6	0	6 (1.0)
Digoxin-Atorvastatin	0	5	5 (0.9)
Digoxin-Colchicine	0	3	3 (0.5)
TOTAL (%)	239 (41.6)	335 (58.4)	574 (100)

Table 8: Types of pharmacokinetics drug interactions with digoxin.

Drug Interactions	Absorption	Metabolism	Excretion	Total (%)
Digoxin-Captopril	-	-	6*	6 (2.5)
Digoxin-Lisinopril	-	-	29*	29 (12.1)
Digoxin-Carvedilol	43	43*	43	129 (54.0)
Digoxin-Spironolactone	-	-	44	44 (18.4)
Digoxin-Nifedipine	-	-	2	2 (0.84)
Digoxin-Amlodipine	-	-	4	4 (1.67)
Digoxin-$CaCO_3$	5	-	-	5 (2.1)
Digoxin-Calcitriol	-	5	-	5 (2.1)
Digoxin-Aspirin	-	-	9*	9 (3.8)
Digoxin-clopidogrel	-	6*	-	6 (2.5)
TOTAL (%)	48 (20.1)	54 (22.6)	137 (57.3)	239 (100)

*Interactions evaluated using drug.com online interaction checkers while others were through Medscape.com online checker.

Table 9: Types of Pharmacodynamics drug interactions with digoxin.

Drug Interactions	Potentiation	synergistic or additive	antagonistic	Total
Digoxin losartan	-	9	-	9 (2.9)
Digoxin-Carvedilol	-	43+43	-	86 (25.7)
Digoxin-Spironolactone	44	44	-	88 (26.3)
Digoxin-bendroflumethiazide	-	11	11	22 (6.7)
Digoxin-$CaCO_3$	-	5	-	5 (1.5)
Digoxin-Frusemide	-	51	51	102 (30.4)
Digoxin-Atenolol	-	2+2	2	6 (1.8)
Digoxin-Aspirin	-	9	-	9 (2.9)
Digoxin-Atorvastatin	5	-	-	5 (1.5)
Digoxin-Colchicine	3	-	-	3 (0.9)
TOTAL (%)	52 (15.5)	219 (65.4)	64 (19.1)	335 (100)

Table 10: Classification of Significant/severity of digoxin Interactions.

Drug Interactions	Minor (%)	Moderate (%)	Severe (%)	TOTAL (%)
Digoxin-Captopril/Lisinopril	0	35	0	35 (14.8)
Digoxin Losartan	0	9	0	9 (3.8)
Digoxin-Carvedilol	0	43	0	43 (18.2)
Digoxin-Spironolactone*	44(*)	44	0	44 (18.6)
Digoxin-Bendroflumethiazide	0	11	0	11(4.7)
Digoxin-Calcium carbonate	0	0	5	5 (2.1)
Digoxin-Calcitriol	0	5	0	5 (2.1)
Digoxin-Furosemide	0	51	0	51 (21.6)
Digoxin-Atenolol	0	2	2	4 (1.7)
Digoxin-Nifedipine	0	6	0	6 (2.5)
Digoxin-Aspirin	0	9	0	9 (3.8)
Digoxin-clopidogrel	0	6	0	6 (2.5)
Digoxin-Atorvastatin	0	5	0	5 (2.1)
Digoxin-Colchicine	0	0	3	1(0.4)
TOTAL (%)	**44 (*)**	**226 (95.8)**	**10 (4.2)**	**236 (100)**

*Some online interaction checkers viewed spironolactone as minor while others viewed it as moderately significant possibly because of its multiple modes of interactions with digoxin.

Table 11: Clinical Outcome of Digoxin Interactions with Other Medications.

S/No.	Potential effects of interaction of digoxin with other drugs	Freq.	%
1.	Agents that may increase serum level or effects of digoxin	121	19.5
2.	Agents that may increase digoxin effects through synergism	61	9.8
3.	Agents that may cause false elevation of digoxin assay	44	7.1
4.	Agents that have serious or very significant interaction with digoxin	10	1.6
5.	Agents whose bradycardiac effects may be enhanced by digoxin	45	7.2
6.	Agents that may enhance AV block	6	1.0
7.	Agents that may enhanced arrhythmogenic effects of digoxin	5	0.8
8.	Agents that may enhance adverse/toxic effects of digoxin	62	10.0
9.	Agents that may decrease the therapeutic effects of digoxin	44	7.1
10.	Agents that digoxin can affect its serum concentrations	3	0.5
11.	Agents that can decrease the excretion of digoxin	90	14.5
12.	Agents that may decrease the metabolism of digoxin	51	8.2
13.	Digoxin combination that may increase concentrations of K^+	18	2.9
14.	Digoxin combinations that may cause some electrolytes problems	62	10.0
	TOTAL	622	100

Table 12: Needed Intervention in Digoxin Interaction with Other Medications.

S/No.	Intervention Required	Freq.	%
1.	Agents combined with digoxin that require digoxin monitoring	154	50.3
2.	Digoxin combination that may necessitate dose reduction by 15-30%	98	32.0
3.	Digoxin combination that may necessitate dose reduction by 30-50%	29	9.5
4.	Agents combined with digoxin that require to be used with caution	5	1.6
5.	Digoxin interactions rated severe and should have been avoided	10	3.3
6.	Digoxin interactions that should have required using alternative agents	10	3.3
	TOTAL	306	100

RESULTS

The mean age and standard deviation in the study is 43.6 ± 20.2 years. The proportion of male to female was 1: 1.77. A high proportions of the patients 179(78.5%) are married while the rest are single 34(14.9%) and widow 15(6.6%). A total of 215(94.3%) has one level of education or the other while 13(5.7%) are uneducated. Unemployment was observed in 138(60.5%) patients compared to 79(34.9%) who are employed with only 11(4.8%) as retiree. Smokers and non-smokers are 10(4.4%) and 218(95.6%) respectively. A total of 155(68.0%) are non-exerciser while 8(3.5%) and 65(28.5%) are regular and non-regular exercisers respectively (Table 1).

Of all the comorbid conditions, the use of digoxin was significantly different from similar patients who do not use digoxin in hypertension (X^2=17.38; P<0.001); anaemia (x^2=4.97, p=0.026); CKD (x^2=10.37, p<0.001) and stroke (x^2=10.54, p<0.001) but not significant with arthritis, dyslipidaemia, migraine, tuberculosis, obesity, hypothyroidism and CAD (p> 0.05)-Table 3.

Digoxin was recommended to 71(31.1%) patients and was combined with loop diuretic in 51(22.4%) cases. Other drug combinations with digoxin are potassium sparing diuretic 44(19.3%), thiazide diuretic 11(4.8%), carvedilol 43 (19.7%), ACEI 35(15.4%), ARB 9(3.9%), calcium channel blocker 6(2.6%), anti-platelets 15(6.6%), haematinics 20(8.8%), while with statins, antacid and calcitriol were 5(2.2%) each; and with anti-gout/arthritis medications 3(1.3%)-Table 4.

The number of drugs interacting with digoxin per prescriptions ranges from one to six. Only 71 (31.1%) prescriptions contain drug interactions with digoxin while 157 (68.9%) do not. Digoxin interactions with one drug and with four drugs per prescription occurred in equal proportions of 11(4.8%) each. Similarly its interactions with five or six drugs per prescription occurred in equal proportions of 1(0.4%) each but its interactions with two or three drugs per prescription were 23(10.1%) and 24(10.5%) respectively (Table 5).

Table 6 showed specific drug interactions with digoxin. A cumulative total of 574 interactions were identified in the study. Carvedilol and spironolactone accounted for the highest multiple of interactions (being 4 each). Atenolol has tripled multiple interactions with digoxin while bendroflumethiazide, calcium carbonate, furosemide and aspirin were all in the multiple of 2 each. All other agents occurred as single interaction.

Of the 574 cumulative interactions of digoxin used by 71 of the 228 patients, 239 (41.6%) were pharmacokinetics interactions in nature while 335 (58.4%) are pharmacodynamics types of interactions. Carvedilol 129(54.0%) accounted for the majority of pharmacokinetic interactions while furosemide 102(30.4%) accounted for majority of

pharmacodynamics interactions with digoxin (Table 7). Of the 239 pharmacokinetics interactions, absorption, metabolism and excretion accounted for 48(20.1%), 54(22.6%) and 137(57.3%) respectively (Table 8) while of the 335 pharmacodynamics interactions; potentiation, synergism/addictive and antagonistics interactions accounted for 52 (15.5%), 219(65.4%) and 64(19.1%) respectively (Table 9).

A total of 622 clinical outcomes were derived from the interaction between digoxin and other medications, which include: increase in serum levels of digoxin 121(19.5%), increase in digoxin effects through synergistic effect 61(9.8%), increased bradycardiac effects 24(7.2%), enhanced AV block 6(1.0%), enhanced arrhythmogenic effects, 5(0.8%), false elevation in digoxin assay 10(1.6%), enhanced adverse effects/toxicity of digoxin 62(10.0%), decreased therapeutic effects of digoxin 44(7.1%), decreased excretion of digoxin 90(14.5%), decreased metabolism of digoxin 51(8.2%), increased K^+ levels 18(6.2%) and other electrolytes problems 62 (10.0%)-Table 11.

Several interventions will be needed such as monitoring digoxin 154(50.3%), dose reduction by 15-30% of digoxin 98(32.0%) or even by 30-50% 29(9.5%), exercising caution in digoxin use 5(1.6%), and total avoidance or use of alternative agents 10(3.3% each)-Table 12.

DISCUSSION

According to current guidelines, digoxin may be used in combination with beta-blockers and/or ACE inhibitors/angiotensin receptor blockers (ACEIs/ARBs) in the management of CHF because it improves symptoms, quality of life, and exercise tolerance in patients with mild-to-moderate HF.[14] Digoxin is a drug with narrow therapeutic levels and as such many drugs can easily alter its pharmacokinetics or pharmacodynamics activities, which easily prone the users into its toxicity. This necessitates the need for close monitoring during pharmaceutical and therapeutic cares in order to prevent the adverse effects that might arise from its utilization. Digoxin is also often combined with several classes of drug like diuretics, ACEI, and BB for symptomatic relief of HF patients, and with other drugs used in the managements of comorbid conditions.[14,15]

In this present study, digoxin is used across various age bands in nearly one-third of patients with CHF but the proportion of users are higher in those above the age of 40 years compared to those who are under 40 years of age. Non-users of digoxin are however significantly different from digoxin users when evaluated across the various age bands (X^2=18.798; p=0.009). Although most of the current guidelines in CHF management do not make digoxin as first line of treatment but as add on to beta-blockers or ACEI/ARB, but digoxin is required for the symptomatic relief of heart failures in association with atrial fibrillation, which may have accounted for the variation in its usage. This pattern of use is however not surprising since some the elderly population appears to gain comparable benefits as does a younger population from the use of digoxin for heart failure management in terms of symptom improvement and reduction of hospitalization.[16]

Among the various types of comorbid diseases identified in CHF patients viz: hypertension, anaemia, CKD and stroke, digoxin use for CHF management was significantly different from patients who do not use digoxin having similar comorbid conditions (Table 3). The use of digoxin with other medications for comorbid conditions like arthritis, dyslipidaemia, arrhythmias, migraine tuberculosis, obesity and hypothyroidism were not significantly different from patients with similar comorbid conditions who are not placed on digoxin. Our results may have indicated that based on these patterns of digoxin utilization in the region, close attention must be paid when a CHF patients presents with some specific comorbidities.

Anemia in heart failure is one of the most common comorbidities and may results due to haemo-dilution, absolute or functional iron deficiency, activation of the inflammatory cascade, and impaired erythropoietin production and activity. Although several therapeutic options are used alone or in combinations with the aim of improving the hemoglobin levels and tissues' oxygenation, but iron therapy, erythropoiesis-stimulating agents, and blood transfusions are most times the available options. In this present study, out of 51 patients recommended for iron containing medications, a minority of patients 9(3.9%) were co-used with digoxin. The OR value for cohort patients on ferrous sulfate is1.116 (95% CI=0.833-1.495).

Diuretics are among the most frequently prescribed drugs in CHF patients, given to the majority of heart failure (HF) cases,[17] and are recommended for patients with symptomatic heart failures. The therapeutic benefits of such combinations is to allow the diuretic particularly the high ceiling ones to control pulmonary congestion and peripheral oedema in accordance with the current guidelines.[13,18] while digoxin improves ejection fraction. Interaction between digoxin and diuretics is common in clinical setting.[19,20]

However there are interactions between the two agents. Furosemide depletes the electrolytes levels particularly K, Mg, Na, Cl and so on. The depletion in K^+ levels increases digoxin toxicity. In this study, close to one-quarter of the patients are at potential risk of digoxin toxicity due to its co-administrations with furosemide and few others may have similar interactions problems with thiazide combinations in their medications. Wangs and associates indicated that the concomitant use of digoxin with a combination of loop diuretics, thiazide and potassium-sparing diuretics carries a varying degree of risks and that the combined therapy of digoxin with

any diuretic is associated with a 3.08-fold increase in the risk of digoxin intoxication.[21] Digoxin toxicity is expected to be greatly enhanced if these diuretics cause hypocalaemia and hypomagnessemia and therefore all patients on digoxin taking diuretic must be closely monitored for these electrolytes imbalances as well as symptoms of toxicity of digoxin.

This study has also identified close to one-fifth of patients at potential risk of having bradycardia through the addictive cardiac effects of digoxin and carvedilol or with atenolol combinations if not monitored. The potential danger arising from such combination is that it can lead to slow in AV conduction and decreased heart rate. While beta-blockers like carvedilol are important components of medications recommended to some CHF patients who may also be taking digoxin because the agent improves left ventricular ejection fraction (LVEF) in patients with chronic heart failure,[22] close monitoring due to these interactions is required. The combination of the two agents has caused digoxin toxicity in children because the clearance of digoxin was decreased by half and carvedilol further increases serum concentrations of digoxin.[23] All patients with such combinations in this present study would therefore require several therapeutic approaches such as decreasing the dose of digoxin, monitoring the levels, monitoring toxicity and ECG monitoring as well. The mechanism through which the combination can cause increased systemic bioavailability of digoxin is through enhanced absorption and reduced renal excretion of digoxin, a pharmacokinetic interaction that is brought about by the inhibition of intestinal and renal P-glycoprotein efflux transporter by carvedilol.

Other agents interacting with digoxin also have the potentials to cause increase in serum digoxin levels and thereby increasing the risk of toxicity. These drugs include atorvastatin, nifedipine, NSAIDs, aspirin, amlodipine, atenolol, captopril, clopidogrel, lisinopril, and losartan. For instance, spironolactone would decrease the renal excretion of digoxin as well as reducing the plasma clearance of digoxin. Agents like aspirin, lisinopril, and atenolol are also capable of decreasing digoxin excretion thereby increasing its serum concentrations. Agents like clopidogrel, carvedilol interact with digoxin to increase the serum levels of digoxin because they decrease the metabolism of digoxin. Furosemide and thiazides, will prone patients into hypokalaemia with resultant digoxin toxicity.

Many pharmacokinetics interactions of digoxin are likely to occur in the study, particularly during its metabolism. Our drug interaction checkers showed that close to one-fifth patients who used carvedilol, and a few patients on clopidogrel may have their digoxin metabolism decreased. While agents like aspirin, atenolol, and lisinopril co-used with digoxin may decrease the excretion of digoxin. When all the drugs used in this study were evaluated using several interaction checkers, there was no reports of pharmacokinetics interactions affecting drug distributions of digoxin. However, drug synergistic effects that would lead to an increased risk of cardiac arrhythmias are expected to occur in few patients due to co-administration of digoxin with medications like calcium carbonates. Many agents will lead to pharmacodynamics synergism with digoxin co-used. Agents affected in this category are bendrofluemethiazide, carvedilol, calcium carbonate and atenolol.

Paradoxically, while digoxin combinations with some agents like ASA, losartan, captopril, spironolactone, and carvedilol may cause addictive increase in K^+ levels, its interaction with agents like furosemide, thiazide causes antagonism in K^+ levels as digoxin increases K^+ levels while these agents lowers it. In either case, K levels must be keenly monitored to avoid hyperkalemia or hypokalemia.

In our study, various drug interaction software checkers like Drug.com, Medscape, Epocrates etc were used but we are careful not to duplicates reported mode or form or outcome reported by other checkers. We cross examined each drug that was co-used with digoxin by every patients and drug combination in other to report areas not reported by one checker. On the basis of this we found about 14 different possible forms of outcomes from 71 (31.1%) patients who used digoxin with other medications. These 14 outcomes cumulated to a total 622 issues in all drug interactions with digoxin. Some of the potential problems that may arise in small proportions were those that may increase the potassium levels when combined with digoxin, medications that enhanced the arrhythmogenic effect of digoxin and medications that may enhance AV block of digoxin were observed.

Of these 622 potential problems identified from various drug combinations with digoxin, close to one-quarter of these will potentially increase the serum concentrations of digoxin thereby increasing its toxicity. A little above one-tenth of these outcomes will have direct effects on the heart but the therapeutic effects of digoxin may be decreased due to some combinations that enhanced digoxin metabolism. Digoxin concentrations may further be increased to toxic level with combinations that decrease digoxin excretion and this occur in high cases while its metabolism will be decreased in about one-tenth of the overall outcomes. In our study, we have observed that not only do other drugs affect digoxin, digoxin also causes changes to few drugs used in combination with it to increase parameter like the serum levels of K^+ and other electrolytes problems may independently results with some combinations.

There is a need for pharmacist's interventions services due to problems arising from several combinations. Among the key interventions required is monitoring of digoxin plasma levels so as to maintain its therapeutic range and prevent its toxic levels, and this may be desired in high proportion of the various combination.

The monitoring will obviously fall under the categories of symptomatic monitoring for toxicity and pharmacokinetic monitoring of the plasma levels. Owing to the ability of other drugs to increase the serum concentrations of digoxin, one of the checkers recommended digoxin dose reduction by up to one-third the usual dose in some combinations while many other combinations may require such similar reductions in up to half of digoxin normal dose. None of the interaction checkers however recommended avoidance or use of alternative agents in all the drug combinations with digoxin that were evaluated in this study.

Although we do not carry out symptomatic follow up in the study to report actual effects of drug interactions with digoxin, literature reports that digoxin interactions may be influenced by age, gender, comorbid diseases and medications used for them, electrolytes levels, medications. These factors may further compound the interaction problems. Some authors have advised that digoxin dosing needs to be personalized based on multiple patient-specific considerations, including age, renal function, body habitus, comorbid conditions, and medications, and that high level of suspicion for chronic toxicity should be maintained in patients using digoxin, especially in women, in those with renal impairment, and in older, frail individuals.[24]

CONCLUSION

Digoxin interactions with medications used to manage CHF patients and other comorbid diseases are diverse and wide. The key outcomes reported from various interaction checkers used are those increasing the serum levels of digoxin thereby increasing their toxicity. Other combinations are capable of enhancing AV block, enhancing digoxin toxicity; enhance the arrhythmogenic effects of digoxin and those that may decrease the therapeutic effects of digoxin. Both pharmacokinetics and pharmacodynamics modes of interactions were identified. These patients would therefore require several therapeutic approaches such as decreasing the dose of digoxin, monitoring the levels, monitoring toxicities and ECG monitoring as well. The findings in this study underscore the need for keen monitoring and intervention in patients using digoxin.

REFERENCES

1. Grymonpre RE, Mitenko PA, Sitar DS, Aoki FY, Montgomery PR. Drugs associated hospital admissions in older medical patients. J Am Geriatr Soc., 1988; 36: 1092–8.
2. Jankel CA, Speedie SM. Detecting drug interactions: A review of the literature. DICP., 1990; 24: 982–9.
3. Jankel CA, McMillan JA, Martin BC. Effect of drug interactions on outcomes of patients receiving warfarin or theophylline. Am J Hosp Pharm., 1994; 51: 661–6.
4. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18820 patients. BMJ., 2004; 329: 15–29.
5. Becker ml, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. Hospitalization and emergency department visits due to drug-drug interactions: A literature review. Pharmaco Drug Saf., 2007; 16: 641–51.
6. Nolan PE Jr, Marcus FI Cardiovascular Drug Use in the Elderly. Am J Geriatr Cardiol, 2000 May; 9(3): 127-129.
7. Patel VK, Acharya LD, Rajakannan T, Surulivelrajan M, Guddattu V, Padmakumar R Potential drug interactions in patients admitted to cardiology wards of a south Indian teaching hospital Australas Med J., 2011; 4(1): 9-14.
8. Hirsch AT, Dzau VJ, Creager MA. Baroreceptor function in congestive heart failure: effect on neurohumoral activation: effect on neurohumoral activation and regional vascular resistance. Circulation, 1987; 75: IV36–48.
9. Gheorghiade M, Ferguson D. Digoxin. A neurohormonal modulator in heart failure? Circulation. 1991;84:2171–86
10. Pervaiz MH, Dickinson MG, Yamani M. Is digoxin a drug of the past? Cleve Clin J Med, 2006; 73: 821–34.
11. The Digitalis Investigation Group. The effects of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med, 1997; 336: 523–33.
12. Hood WB, Jr, Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis. J Card Fail, 2004; 10: 155–64.
13. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur J Heart Fail, 2008; 10: 933–89.
14. Yancy CW, Jessup M, Bozkurt B, et al. 2013ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*, 2013; 128: e240-e327.
15. Fuster V, Rydén LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Circulation*, 2001; 104: 2118-2150.
16. Cheng JW, Rybak I. Use of digoxin for heart failure and atrial fibrillation in elderly patients. Am. J. Geriatr. Pharmacother, 2010 Oct; 8(5): 419-27.
17. Bennett S. Diuretics: use, actions and prescribing rationale. Nurse Prescribing, 2008; 6: 72–7.
18. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini

DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation, 2009; 119: 1977–2016.

19. Janchawee B, Wongpoowarak W, Owatranporn T, Chongsuvivatwong V. Pharmacoepidemiologic study of potential drug interactions in outpatients of a University hospital in Thailand. J Clin Pharm Ther, 2005; 30: 13–20.
20. Magro L, Conforti A, Del Zotti F, Leone R, Iorio ML, Meneghelli I, Massignani D, Visonà E, Moretti U. Identification of severe potential drug-drug interactions using an Italian general-practitioner database. Eur J Clin Pharmacol, 2008; 64: 303–9.
21. Wang M-T, Su C-Y, Chan A.L.F , Lian P-W, Leu H-B, and Hsu Y-J: Risk of digoxin intoxication in heart failure patients exposed to digoxin–diuretic interactions: a population-based study Br J Clin Pharmacol, 2010 Aug; 70(2): 258–267.
22. Keating GM, Jarvis B: Carvedilol: a review of its use in chronic heart failure. Drugs., 2003; 63(16): 1697-741.
23. Ratnapalan S, Griffiths K, Costei AM, Benson L, Koren G. Digoxin-carvedilol interactions in children. J Pediatr, 2003; 142(5): 572-4
24. MacLeod-Glover N, Mink M, Yarema M, Chuang R. Digoxin toxicity Case for retiring its use in elderly patients? Can Fam Physician, 2016 Mar; 62(3): 223–228.